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Pure polyphenols applications for cardiac health and disease

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Abbreviations : AMP-activated protein kinase, AMPK; activating transcription factor 6, ATF6; Angiotensin I converting enzyme, ACE; B-cell lymphoma 2, BCL-2; Bcl-2-associated X, BAX; BCL-2 adenovirus E1B 19-kDa interacting protein 3, BNIP3; blood pressure, BP; Ca^{2+} /calmodulin-dependent protein kinase kinase β , CaMKK β ; cardiovascular diseases, CVD; CCAAT-enhancer-binding protein homologous protein, CHOP; cyclic nucleotides phosphodiesterases, PDEs; dual specificity protein phosphatase, DUSP; doxorubicin, DOX; endothelial nitric oxide synthase, eNOS; epigallocatechin-3-gallate, EGCG; endoplasmic reticulum, ER; inositol-requiring enzyme-1 α , IRE1 α ; heart failure; HF; extracellular signal-regulated kinase, ERK; flow-mediated vasodilation, FMD; ischemia and reperfusion, I/R; interleukin (IL); hypoxia-inducing factor 1- α , HIF-1 α ; lipopolysaccharide, LPS; lysosome-associated membrane protein 2a, LAMP2a; microtubule-associated protein 1A/1B-light chain 3, LC3; lactate dehydrogenase, LDH; nicotinamide adenine dinucleotide, NAD^+ ; nicotinamide adenine dinucleotide phosphate, NADPH; low density lipoprotein, LDL; nuclear factor of kappa light polypeptide gene enhancer in B-cells, NF- κ B; nuclear factor erythroid-derived 2-like 2, Nrf2; poly (ADP-ribose) polymerase-1, PARP-1; Protein Kinase C, PKC; protocatechuic acid, PCA; phospho-extracellular regulated protein kinases, PERK; randomized controlled trials, RCTs; exchange factor directly activated by cAMP 1, Epac1; rat neonatal ventricular cardiomyocytes, RNVC; reactive oxygen species, ROS; salvianolic acid B; SalB; sirtuin 1, SIRT1; specific protein 1, SP1, superoxide dismutase, SOD; theaflavin-3,3'-digallate, TF3; tumor necrosis factor (TNF- α); telomere repeat-binding factor 2, TRF2; 78 kDa glucose-regulated protein GRP78; 94kDa glucose-regulated protein, GRP94; vascular cell adhesion molecule 1 (VCAM-1); transverse aortic constriction (TAC); c-Jun N-terminal kinases, JNK; xanthine/xanthine oxidase, X/XO; mitogen-activated protein kinase-activated protein kinase 2, MAPK-APK-2; heat shock protein 27, HSP27; activator protein 1, AP-1; systolic blood pressure, SPB; diastolic blood pressure, DBP; high density lipoprotein, HDL; isoproterenol, ISO; phosphatidylinositol-3-kinases, PI3K; protein kinase-B, Akt; signal transducer and activator of transcription 1, Stat1; sensitive potassium channels, KATP; cGMP-dependent protein kinase or Protein Kinase G, PKG; toll-like receptor 4, TLR4; vascular endothelial growth factor, VEGF; intercellular adhesion molecule-1, ICAM-1;

Abstract

Polyphenols are natural compounds presents in fruits and vegetables that can exert beneficial effects on human health and notably, on the cardiovascular system. Some of these compounds showed significant protective activities toward atherosclerosis, hypertension, myocardial infarction, anthracyclin-induced cardiomyopathy, angiogenesis as well as heart failure. Polyphenols can act through systemic effects as well as through modulation of signaling pathways such as redox signaling, inflammation, autophagy and cell death in the heart and vessels. These effects can be mediated by changes on expression level and by post-translational modifications of proteins (e.g. Stat1, CaMKII, Sirtuins, BCL-2 family members, PDEs, TRF2, eNOS and SOD). This non-comprehensive short review aims to summarize recent knowledge on the main pharmacological effects and mechanisms of cardioprotection of pure polyphenols, using different approaches such as cell culture, animal models and human studies.

1. Introduction

Nowadays, cardiovascular diseases (CVD) constitute a major health problem and have become the largest single contributor worldwide of non-communicable deaths accounting for more than 50% [1]. CVD are a group of disorders affecting the heart and blood vessels, and include diseases and/or syndromes such as atherosclerosis, hypertension, ischemic coronary and heart diseases, myocardial infarction and heart failure (HF) [1]. Most of these diseases are heterogeneous conditions with diverse etiologies and comorbidities, generally aggravated by age and risk factors such as hereditary factors, sex, tobacco, unhealthy diet, physical inactivity, cholesterol, alcohol and hypertension (Figure 1). Due to their prevalence and their anticipated increase in the next decade, the study of CVD and the search for better prevention and treatments have recently regain interest in academic and pharmaceutical sectors.

CVD share common pathological mechanisms, but each pathology has also its own specificities, mechanisms and comorbidities. Thus, it is admitted that myocardial infarction results from events of ischemia and reperfusion (I/R) affecting the blood flow through vessels and the heart [2]. Most of the time, this implies four sequential phases of vascular and cardiac alterations: (i) development of atherosclerotic plaque within the vessel, (ii) atherosclerotic plaque rupture and thrombosis, (iii) acute tissue and cellular damage due to the reperfusion of the heart following ischemia and (iv) chronic tissue remodeling. These phases are also associated with hypertension, cardiac hypertrophy, oxidative stress, inflammation, cell death and fibrosis. All these damages contribute ultimately to cardiac dysfunction with a decrease in ejection fraction and can lead to arrhythmias. This cardiac remodeling can evolve during several years and can lead to HF, acute decompensated HF and ultimately patient death [2]. Of note, HF and congenital cardiomyopathies can also occur independently of myocardial infarction depending on patient history and risk factors (Figure 1).

Due to their complexity, heterogeneity and co-morbidities, CVD are difficult to treat, and drug combinations are frequently necessary to address the various causes and symptoms. For example, irrespective of specific country health rules, a variable combination of vasodilators, beta-blockers,

angiotensin-converting enzyme inhibitors, diuretics, aldosterone antagonists, inotropes and thrombolytics are recommended to treat CVD patients.

Strong evidence from observational studies and meta-analyses have revealed a positive correlation between greater intake of fruits and vegetables and a decreased prevalence of CVD [3]. Fruits and vegetables are characterized by low caloric density and can provide dietary fibers, essential vitamins and minerals, which are beneficial nutrients and low-energetic constituents. Moreover, they are exclusive and rich sources of a wide variety of phytochemicals, including polyphenols, carotenoids, plant sterols, and glucosinolates. Although not strictly essential micronutrients, some of these phytochemicals can contribute to a healthy body weight, desirable lipid profile and blood pressure (BP) [4, 5]. Understanding which are the most promising cardioprotective compounds in the diet is therefore of great interest to international health organizations and governments, in order to plan public health strategies and interventions to combat the growing global CVD burden [1].

In this context, polyphenols have been proposed to exert beneficial effects on the prevention of CVD and treatment via ability to prevent them and favor repair processes of heart and vessels. Indeed, research undertaken during the last decades demonstrated that they can have pleiotropic roles in controlling cardiac apoptosis, inflammation, endothelium integrity and oxidative stress [2, 6]. The underlying mechanisms are believed to include effective inhibition of low density lipoprotein (LDL) oxidation, a key process in the onset of atherosclerosis [7]. In addition, polyphenols have beneficial effects on platelet aggregation and thus participate to the regulation of BP [8]. Moreover, certain polyphenols prevent pathological cardiac remodeling, which includes effects on cardiac hypertrophy, cardiac dilatation and fibrosis [9]. Altogether, despite the fact that numerous cellular and molecular mechanisms remain unknown, some studies support that polyphenols play a critical role in cardioprotection [10].

Polyphenols are natural compounds largely found in plants (Figure 2). They are characterized by the presence of one or several phenolic groups linked to one hydroxyl functional group (-HO) that can be associated into complex structures [9, 11]. Not all present structural characteristics of polyphenols but are commonly integrated in the group of polyphenols as “honorary”, which is the case of phenolic acids and stilbenes [12-14]. Polyphenols are an extremely diversified group in terms of chemical structure.

They include 4 classes, namely flavonoids, stilbenes, phenolic acids and lignans and 6 sub-classes of flavonoids, including flavonols, flavones, flavanones, flavanols, isoflavones and anthocyanins [11]. From almost all classes, compounds with cardioprotective properties have been identified. A scheme of the polyphenol classification and the chemical structure of main compounds that are discussed in the review are presented in figure 2.

Polyphenols have been studied either in a pharmacological or nutritional perspective for their influence on CVD [15, 16]. Some meta-analysis of randomized controlled trials (RCTs) confirmed the validity of individual studies, with particularly strong evidence existing for cocoa and tea flavanols [17-19]. Of note, the polyphenols most commonly ingested in the human diet are not necessarily the most active within the body. The extensive and rapid metabolism to which dietary polyphenols are submitted once ingested, either in the gastrointestinal tract, microbiota, liver, and or in cells, leads to the appearance of a broad range of new polyphenol metabolites. In order to assess the efficacy of polyphenols, and to be able to use them as therapeutic molecules, it is important to conduct studies with pure or purified compounds. Recently, novel strategies to supply pure polyphenols to humans and avoid their extensive metabolism have been emerging since there is increasing evidence of their pharmacological potential. Formulations and methods for enhancing polyphenols bioavailability, solubility and stability in the human body have been patented, creating new derivatives with improved biological activity and stability [20]. Besides the form of delivery/route of administration, administration of pure compounds is an attractive alternative to the use of mixtures or whole extracts in a pharmacological perspective, even if very few human trials have been conducted with the various classes of polyphenols as pure compounds.

The aim of this review is to highlight and discuss some recent knowledge on cellular, animal and human studies conducted with pure polyphenols to delineate their main pharmacological mechanisms of cardioprotection and identify their putative targets. We will not address nutritional studies where the effect of dietary polyphenols in foods are considered, or the effect of nutritional relevant polyphenol metabolites in cellular system, or polyphenols ability to induce epigenetic modifications, since it is beyond the scope of this review. Moreover, we will not discuss exhaustively isolated heart studies, because systemic effects cannot be addressed with this model, and they are poorly predictive of *in vivo*

effects, due to metabolic transformation of compounds. For a better understanding, we divided the review in the different classes of polyphenols, i.e. flavonoids, stilbenes, phenolic acids and lignans as introduced in Figure 2 and for each class, we discuss the effects described for the most representative compounds studied *in vitro*, *in vivo* and in human trials.

2. Flavonoids

2.1. Flavonols

Flavonols are one of the classes of polyphenols that are widely distributed in plants, and are present usually as diverse glucosides, in considerable amounts in onions, apples, cider, grapes, wine and tea. They derive from 3-hydroxyflavone, and the simplest flavonol, quercetin, is the most abundant in plants and the best studied flavonol in human health [21]. Quercetin cardioprotective properties were extensively studied in cellular, animal and even in humans (Table 1).

Flavonols interfere with a large number of biochemical signaling pathways and, therefore, physiological and pathological processes. There is solid evidence that, *in vitro*, quercetin and related flavonols exert endothelium-independent vasodilator effects, protective effect on nitric oxide and endothelial function under conditions of oxidative stress, anti-platelet aggregation effects, inhibition of low density lipoprotein (LDL) oxidation, reduction of adhesion molecules and other inflammatory markers [21]. Plasma isolated from animals, submitted to a widely accepted non-lethal mechanical trauma, was used to induce stress in H9c2 cells, a rat cardiomyoblast cell line. Pretreatment with quercetin (20 μ M; 24 h before trauma, plasma addition) significantly attenuated trauma-induced viability decrease, tumor necrosis factor alpha (TNF- α) increase, reactive oxygen species (ROS) overproduction and $[Ca^{2+}]_i$ overload in H9c2 cardiomyocytes [22]. Another study showed that pretreatment with quercetin before I/R could increase H9c2 cells survival. Quercetin significantly alleviated I/R-induced phosphorylation of c-Jun N-terminal kinases (JNK) and p38, which further increased B-cell lymphoma 2 (BCL-2) expression and inhibited the activation of *Bcl-2*-associated X (BAX) and caspase-3 [23].

One suggested marker for heart diseases in patients with chronic isolated mitral regurgitation and ejection fraction >60% is the increased activity of xanthine/xanthine oxidase (X/XO) [24] and it has been suggested that some polyphenols exhibit cardioprotection via an effect on X/XO. Thus, to

understand the mechanisms underlying cardioprotective effect of quercetin, the expression levels of stress-responsive proteins were studied in X/XO-induced toxicity model of H9c2 cardiomyocytes. Pretreatment with quercetin (0.1-10 $\mu\text{g/ml}$; 24 h) enhanced viability and inhibited ROS generation in a 12h exposure to a free radical generating system X/XO. Moreover, X/XO increased the phosphorylation of downstream substrate of p38, mitogen-activated protein kinase-activated protein kinase 2 (MAPK-APK-2), p44/42-MAPK (Erk1/2) and cleaved caspase-3 but inhibited the levels of phosphorylated c-Jun and heat shock protein 27 (HSP27). Pretreatment with quercetin attenuated the phosphorylation of MAPK-APK-2 and cleaved caspase-3 in X/XO-exposed cells [25].

Quercetin plays also a role in the inhibition of angiotensin II-induced H9c2 cells hypertrophy by enhancing peroxisome proliferator-activated receptor gamma (PPAR- γ) expression and suppressing activator protein 1 (AP-1) transcription factor activity [26]. The quercetin's anti-hypertrophic effect has been confirmed in neonatal cardiomyocytes by modulation of protein kinase C (PKC) and tyrosine protein kinase activities [27].

In parallel, quercetin protected also primary cultures of rat cardiomyocytes and H9c2 cells against the anticancer agents doxorubicin (DOX) and daunorubicin, well-known to induce acute and long-term cardiotoxicity [28-31].

When administered in a pure form in rats, quercetin limited cardiac hypertrophy and prevented cardiac dysfunction and hypertension in several rat models of transverse aortic constriction (TAC) and models of hypertension [32-35]. Moreover, one week after TAC and following intragastrical administration for 6 weeks, the effects of quercetin and the flavanol epigallocatechin-3-gallate (EGCG, see below) were compared individually to those of three drugs, namely AT1 receptor blocker losartan, angiotensin I converting enzyme (ACE) inhibitor, captopril and beta receptor blocker, carvedilol, for protection against abdominal aortic constriction, a recognized model of pressure overload-induced cardiac hypertrophy [36]. In this model, malondialdehyde contents progressively increased, while superoxide dismutase (SOD) activities decreased. Cardiomyocyte apoptosis, telomere attrition, modulation of p53, c-MYC and of the antiapoptotic protein BCL-2 were also evaluated. Interestingly, all compounds reduced cardiac hypertrophy and cardiomyocytes apoptosis, but they had different effects on apoptotic-related proteins BCL-2, p53 and c-MYC, known to promote cell proliferation and cell death when

overexpressed [37]. EGCG, quercetin and carvedilol promoted the reduction of malondialdehyde (MDA) contents and resumption of SOD activities. Moreover, these 3 compounds could prevent telomere attrition and telomere repeat-binding factor 2 (TRF2) loss remarkably, whereas compounds such as captopril and losartan had no effect on oxidative stress and telomere [36]. At the molecular level, quercetin mediates a down regulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to a decrease in superoxide generation and an increase in endothelial nitric oxide synthase (eNOS) activity [38]. This might explain, at least in part, how quercetin prevents endothelium dysfunction in hypertensive rats [8] and cardiotoxicity in adriamycin treated mice [39].

A significant amount of clinical studies has investigated the acute and chronic effects of the flavonol quercetin or quercetin-3-*O*-glucoside, with mixed results. A recent meta-analysis investigating the effects of quercetin on BP included 7 trials with a total of 587 patients [40]. Significant reductions in systolic BP (SBP, -3.04 mm Hg) and diastolic BP (DBP, -2.63 mm Hg) were found after supplementation with quercetin. Doses of quercetin equal or higher to 500 mg/day significantly decrease SBP and DBP (-4.45 mm Hg, and -2.98 mm Hg, respectively), whereas no significant effects were shown for doses lower than 500 mg/day. Another meta-analysis of 5 RCT with 442 subjects [41], showed no significant effects on quercetin supplementation on plasma LDL-C, HDL-C or triglycerides with a small significant effect in total cholesterol (3.13 mg/dL). At doses higher or equal to 500 mg quercetin/ day, significant increase in total cholesterol (3.57 mg/dL) and decrease on triglycerides (-24.54 mg/dL) was found. Finally, several studies have investigated the effects of quercetin on endothelial function with conflicting results. Two recent studies investigating the effects of quercetin-3-*O*-glucoside on BP and endothelial function showed no acute effects of 0-400 mg of quercetin-3-*O*-glucoside [42] or chronic effects of daily consumption of 160 mg for 4 weeks [43]. Studies investigating the effects of quercetin supplementation on endothelial function also failed to show an effect, either acute (1095 mg of quercetin) [44] or after 8 weeks supplementation of 150 mg/ day of quercetin [45]. Other common flavonols include kaempferol, myricetin, isorhamnetin, tamarixetin, morin and fisetin (for review :[21]) and as quercetin, whether these compounds effects have been characterized *in vitro*, more proof that they can protect from cardiovascular diseases *in vivo* are awaited.

2.2 Flavones

Flavones are potent molecules mainly found in cereals and herbs. Pure flavones have been evaluated for their pharmacological effects on cardiac cell including H9c2 cells, neonatal rat ventricular cardiomyocytes or atrial cells. Whether many of them exert , anti-inflammatory, anti-apoptotic activities and protect from oxidative stress, many others also show a ion channel modulatory activity or anti hypertrophic activity, which may be particularly important in terms of cardiac function [46-50]. Reportedly, dietary flavones exert direct vasorelaxing activities [51, 52], but studies evaluating the activity of pure flavones are scarce. Apigenin, acacetin and scutellarin are 3 examples of the most studied flavones (Table 2)

Apigenin is described to reduce the inflammatory process induced by lipoteichoic acid in rat cardiomyoblast cells [53]. In rats apigenin (50 and 75 mg/kg/day; i.p. for 14 days and ISO (100 mg/kg, s.c.) on 13th and 14th days for initiation of cardiotoxicity), attenuated cardiac damages following β -receptor-stimulated myocardial injury. Apigenin induced protection was associated with effects on antioxidant classical markers, i.e. creatine kinase-MB isoenzyme, glutathione, superoxide dismutase and catalase and malondialdehyde levels [54].

Acacetin revealed to be an atrium-selective agent, effectively diminishing atrial fibrillation in anesthetized dogs [55]. Moreover the authors also demonstrate that acacetin selectively inhibits human atrial repolarization potassium currents [55].

An interesting flavone is scutellarin, which is used in traditional Chinese medicine for the treatment of various conditions including cardiovascular diseases. Among various activities (Table 2), scutellarin could influence positively vascular health via an effect on inflammation in human endothelial cells (ECV304 cells) [56]. However, all the mechanistic aspects of its bioabsorption and metabolism in humans are still under investigation [57].

2.3 Flavanols

Monomeric flavanols, such as catechin, epicatechin, epigallocatechin, gallocatechin, and their gallate derivatives, and their polymerization products (proanthocyanidins), can be found in cocoa powder, chocolate, teas, and grapes[58].

Flavanols promote cardiomyocyte survival *in vitro* and block cell death in oxidative stress conditions, being these effects well described for EGCG, catechin and epicatechin (Table 3). Moreover, some beneficial effects would be mediated by action on the contractile machinery, voltage-gated channels, Ca^{2+} homeostasis and cell-to-cell communication (Table 3).

The main bioactive compounds found in green tea are epicatechins. Among them, EGCG is the most described and characterized compound. In rat neonatal ventricular cardiomyocytes (RNVC), oxidative stress was induced by lead treatment, causing a decrease in SOD and catalase activities, along with increased intracellular levels of hydroxyl radical, anion superoxide and hydrogen peroxide. These features were reversed by co-treatment with EGCG, indicating its biological cytoprotective property [59]. Likewise, hydrogen peroxide-induced oxidative stress in H9c2 cardiomyocytes promotes apoptosis assessed by chromatin condensation, DNA fragmentation and increased expression of p53 and p21, telomere length shortening and the decrease of protein expression of Trf2, while pre-treatment with EGCG for 24h inhibited telomere-dependent apoptotic pathway induced by hydrogen peroxide [60]. Hydrogen peroxide also alters the expression of adherens and gap junction proteins increasing intracellular ROS and Ca^{2+} levels [61]. These effects were attenuated by pre-treatment with EGCG. Interestingly, proteomic studies demonstrated that EGCG has multiple cellular targets and binds to the 67kDa laminin receptor, caveolin-1 and -3, β -actin, myosin 9 and vimentin. Caveolin would serve as a membrane raft that may help mediate cardioprotective EGCG transmembrane signaling [61]. Moreover, in a high glucose model of arrhythmia in diabetic hearts, EGCG reverted the low levels of connexin 43 expression in a p38 MAPK-dependent manner in RNVC [62]. In addition, I/R is known to trigger oxidative stress and massive cell death during the reperfusion phase. In various cellular models, EGCG proved to have anti-apoptotic properties via the activation of phosphoinositide 3-kinase/protein kinase-B (PI3K/Akt) pathway [63] or via the phosphorylation of signal transducer and activator of transcription 1 (Stat1), known to play a critical role in the induction of cardiomyocyte apoptosis [64]. Nevertheless,

depending on the dose, micromolar *vs* nonamolar range, EGCG can become toxic by acting on ATP-sensitive potassium (KATP) channels [65].

EGCG's beneficial role is not limited to apoptosis inhibition, this compound also modulates Ca^{2+} transients and cardiomyocyte beating. In primary cultures of rat cardiomyocytes, DOX decreased cell beating and Ca^{2+} transients, i.e. the rapid increase of Ca^{2+} in the cell, which peaks and gradually decreases during the cardiac action potential. EGCG increased the amplitude of electrical and caffeine-induced Ca^{2+} transients in DOX-treated cardiomyocytes, indicating that EGCG may limit the DOX-induced Ca^{2+} depletion in the sarcoplasmic reticulum [66]. In another study using EGCG at the nanomolar concentration, similar to the circulating dose in human plasma, Feng and colleagues have demonstrated that EGCG increases contractility of murine cardiomyocytes by increasing electrical-induced Ca^{2+} transients, content of Ca^{2+} in sarcoplasmic reticulum and probability of opening of the ryanodine receptor [67].

Catechin and proanthocyanidin B4 are two flavanols found in grape seeds, which prevent DOX-induced cardiomyocytes death by decreasing ROS generation and limiting DNA fragmentation [68]. Likewise, as other grape polyphenols such as quercetin and resveratrol, catechin could be cardioprotective by inhibiting cardiac voltage-gated sodium channels activity in left ventricular rat myocytes and therefore, preventing cardiac arrhythmias [69]. The IC_{50} of the 3 compounds were 19.4 μM , 77.3 μM and 76.8 μM , respectively. Intriguingly, the absence of blocking effect of *N*-acetylcysteine on this channel suggests that the compounds act independently of their cytoprotective effects [69].

Theaflavin-3,3'-digallate (TF3) present in black tea limited cell death induced by hydrogen peroxide in RNVC, as observed for EGCG [70]. Although TF3 activates extracellular signal-regulated kinase (ERK) 1/2, Akt and p38 mitogen-activated protein kinase, whenever these kinases are inhibited, TF3 is still able to promote cell survival and prevent intracellular ROS accumulation. Thus, kinases are not essential for TF3-mediated cardioprotection [70]. In the same cell model and again in comparison to EGCG, methyl gallate, a methyl ester of gallic acid, inhibits apoptosis by decreasing intracellular ROS generation, increasing reduced glutathione levels and maintaining mitochondrial membrane potential [71].

Epicatechin is considered an important factor associated to the cardiovascular beneficial effects of flavanol-rich foods [72]. Pharmacological studies have found that epicatechin exhibits protective effects on oxidative stress injury, myocardial ischemia reperfusion injury and permanent coronary occlusion [73-75]. Epicatechin treatment also improved mitochondrial structure in enhanced cardiac function in patients with heart failure. However, it is fairly unknown whether epicatechin has a direct effect on cardiac hypertrophy and the mechanism underlying its anti-hypertrophic role remains poorly clarified. A recent study with neonatal mouse cardiomyocytes shown that epicatechin significantly inhibited Ang II-induced increase of cardiomyocyte size by activating the specificity protein 1/Sirtuin 1 (SP1/SIRT1) signalling pathway [76]. Moreover, 1 mg/kg body weight/day epicatechin significantly inhibited mouse cardiac hypertrophy induced by Ang II, which could be eliminated by SP1 inhibition *in vivo* [76].

The flavanols proved their ability to prevent cardiac damages also in several rodents models, at least by increasing antioxidant capacity in the heart and other organs [77, 78] (Table 3). For example, two weeks of administration of epicatechin in drinking water (100 mg/kg/day) prevented BP increase in young spontaneously hypertensive rats and thus, diminished locomotor activity. Underlying mechanisms involved an increase in iNOS activity and a reduction in superoxide production in left ventricle and aorta [77]. When administrated seven days before isoproterenol (100mg/kg, s.c.), EGCG (15mg/kg, i.p.) prevented cardiac damages by maintaining the balance of anti-apoptotic / pro-apoptotic signaling proteins in the mitochondrial pathway of cell death, limiting oxidative stress inflammation, and protecting DNA integrity [78].

Several meta-analysis have confirmed that cocoa flavanol consumption can improve endothelial function and decrease BP. A couple of studies have investigated the effects of the main flavanol monomer present in cocoa, epicatechin, which is believed to be responsible for the cardiovascular health benefits of cocoa intake. Consumption of 1-2 mg of (-)-epicatechin/kg body weight (BW) was shown to acutely improve endothelial function in healthy individuals [72, 79]. In contrast, a recent study by Dower *et al.* did not detect statistically significant long-term changes in flow-mediated vasodilation (FMD) or BP after 4 weeks supplementation with 100 mg of (-)-epicatechin per day [80]. Although more studies

are needed to confirm these contrasting findings, it may be that investigations using a purified dietary constituent do not fully mimic the effects or effect sizes observed when the same constituent is consumed in its native food/food matrix. In a very recent study, Sansone *et al.* [81] reported that cocoa methylxanthines (theobromine and caffeine) enhanced the vascular effects exerted by cocoa flavanols and also improve their bioavailability. This shows that synergistic effects between polyphenols and other dietary compounds exist, which may explain the different effects observed when pure compounds and polyphenol rich foods or extracts were tested. Synergistic effects between cocoa flavanols and dietary nitrate, another food bioactive present in vegetables, have also been shown at dietary achievable amounts [82].

2.4 Flavanones

Flavanones are the major class of polyphenols present in *Citrus* fruit, they include hesperidin, naringenin, eriodictyol among others, and their respective glycosides [83]. Naringenin and its respective glucoside, naringenin-7-*O*-glucoside are the most well studied in cell culture of cardiomyocytes (Table 4). Naringenin has been reported to exhibit cardioprotective effects, namely, anti-inflammatory, hypolipidemic, and anti-atherogenic properties [84]. The treatment of H9c2 cells with pure naringenin was shown to be effective against I/R injury *via* attenuating endoplasmic reticulum (ER) stress or ER stress-mediated apoptosis. Naringenin treatment restored cell viability, cell morphology, normalized BCL-2, BAX and caspase 3 in I/R-treated H9c2 cells. Likewise, the protective effect of naringenin against I/R injury is due to inhibition of ER stress-mediated apoptosis, which potentially involves activation of transcription factor 6 (ATF6), inositol-requiring enzyme-1 α (IRE1 α) and phospho-extracellular regulated protein kinases (PERK) [85]. Thus, pretreatment of H9c2 cells with naringenin promoted the reduction of ER-mediated apoptotic cell death and lipid peroxidation, and showed increased level of reduced glutathione when these cells were submitted to an oxidative insult such as H₂O₂. In addition, gene expression studies revealed that naringenin upregulated the transcription of Akt, nuclear factor erythroid-derived 2-like 2 (Nrf2) and its target genes, and downregulated nuclear factor-kappa B (NF- κ B) and caspase 3 expression. This study suggests that improvement of Nrf2 signaling via

naringenin supplementation would be a rational approach to facilitate ROS detoxification by augmenting both expression and activity of phase II detoxification enzymes, which in turn alleviate cardiac complications [86].

In a very recent study, in a cellular model of senescent myocardial cells, it was observed that naringenin reduce relevant cellular senescence markers (X-gal staining, cell cycle regulator levels, and the percentage of cell cycle-arrested cells). Moreover naringenin modulate cardiac markers of aging-induced damage (e.g. ROS, mitochondrial metabolic activity, mitochondrial calcium buffer capacity, and estrogenic signaling functions). Overall the authors suggest that naringenin has antiaging effects on myocardial cells [87].

Some studies suggest that naringenin and naringenin-7-*O*-glucoside could prevent cardiomyocytes from DOX-induced toxicity by their property of stabilizing the cell membrane and reducing ROS generation, promoting the induction of endogenous antioxidant enzymes via phosphorylation of ERK1/2 and nuclear translocation of Nrf2. These effects could underlie the use of these flavanones as therapeutic agents for treating or preventing cardiomyopathy associated with DOX [30, 88-90].

In mice naringenin is able to exert a protective effect against cardiac hypertrophy induced by pressure overload. Diet supplementation with naringenin attenuated cardiac hypertrophy and interstitial fibrosis, in addition to improving left ventricular function. The cardioprotective effect exerted by naringenin was associated with the inhibition of PI3K/Akt, ERK and JNK signaling pathways[91].

Liu *et al.* showed that naringenin can improve cardiac and renal function in a rat model of cardiorenal syndrome, a complex disorder in which each organ has a deleterious effect on the other. Indeed, naringenin (25 mg/kg/day or 50 mg/kg/day, 4 weeks, oral gavage) attenuated cardiac remodeling and cardiac dysfunction, decreased lipid profiles, inhibited cardiac inflammation and reduced oxidative stress. Nrf2 and/or catalytic subunit of glutamylcysteine ligase-regulated glutathione (GSH) synthesis contributed to naringenin-induced protective effects [92].

Hesperidin found in citrus fruits upon ingestion releases its aglycone, hesperetin that have been studied for cardioprotective activity in *in vitro* systems (Table 4). The post treatment of rat cardiomyocytes submitted to H/R injury with hesperitin inhibited apoptosis by elevating Bcl-2 expression and decreasing Bax and cleaved caspase-3 expression levels. It was observed that this protective effect was

mediated through the activation of PI3K/Akt signalling pathway [93]. Another evidence of hesperetin anti-apoptotic effect was observed in lipopolysaccharide (LPS)-induced H9C2 cells via the JNK/Bax signalling pathway. Hesperitin has a mitochondria-dependent anti-apoptosis effects in these cells by downregulation of Bax and upregulation of Bcl-2 concomitant with the attenuation of JNK phosphorylation [94].

In rats hesperidin (50 mg/kg/day HP, 14 days, oral gavage) was found to protect rat cardiac function treated by the anticancer drug cisplatin, [95]. With a shorter treatment at a higher dose, hesperidin treatment (200 mg/kg hesperidin/rat, 3 days, oral gavage) attenuates myocardial I/R injury by suppressing myocardial apoptosis, the inflammatory response and oxidative stress via PI3K/Akt pathway activation and HMGB1 (high-mobility group box 1) inhibition in rats [96]. In a rat model of left ventricular remodelling, induced by a permanent left anterior descending coronary artery (LAD) occlusion, cardiac dysfunction, myocyte apoptosis and inflammation were significantly attenuated by hesperidin (30 mg/kg/day, oral gavage), via an inhibition of caspase-3 activity, myeloperoxidase expression, α -smooth muscle actin expression, and matrix metalloproteinase-2 activity. In the same study, hesperidin prevented also myocardial infarction-induced ventricular dysfunction and structural remodelling of myocardium [97]. Finally, hesperidin (100 mg/kg/day, oral gavage) proved also to exert beneficial cardioprotective activity in a cardiac I/R injury in diabetic rats when performed a LAD occlusion an effect mediated by PPAR- γ pathway [98].

To date, only 4 studies have investigated the effects of pure hesperidin on vascular function in humans (Table 4). Consumption of 500 mg of pure hesperidin per day for 3 weeks, resulted in significant improvements in endothelial function measured as FMD in subjects with the metabolic syndrome, through NO production [99]. Also, both orange juice and hesperidin capsules (containing both 292 mg of hesperidin) significantly improve acetylcholine-mediated vasodilation 6 h after ingestion on healthy overweight men, and decreased DBP after 4 weeks daily consumption [100]. In contrast, two recent studies have reported no improvements in CVD markers after hesperidin supplementation. An acute study in healthy individuals showed no effects on FMD, BP, or arterial stiffness when 320 mg of hesperidin was given as a pure compound or as an orange juice [101]. In a 6 week study in overweight individuals, 540 mg of hesperidin per day did not improve FMD, BP and other CVD markers [102].

2.5 Isoflavones

Isoflavones have gained considerable attention for their potential role in improving risk factors for cardiovascular disease. Experimental models have used cardiac cells, live animals and were also tested in humans (Table 5). Genistein is an isoflavone present in several plants, including soya, lupin and fava beans. This isoflavone is widely described as a modulator of ionic channels, acting by direct binding or by interfering with key modulatory phosphorylation processes as a tyrosine kinase (TK) inhibitor [103]. Regarding its effects on the cardiovascular system, this compound is able to modify cardiomyocytes function, particularly by modifying Ca^{2+} signalling and homeostasis *via* effects on multiple targets. In guinea-pig myocytes, genistein directly interacts with L-type Ca^{2+} channel, reducing Ca^{2+} currents, and consequently Ca^{2+} influx [104]. However, genistein can also stimulate Ca^{2+} influx in cardiomyocytes by direct interacting with transient receptor potential cation channel 5, TRPC5 [104]. On the other hand, by acting on the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, this isoflavone impairs its ability to extrude Ca^{2+} . Genistein also increases sarcoplasmic reticulum Ca^{2+} load, which may be a cellular compensatory response to $\text{Na}^+/\text{Ca}^{2+}$ exchanger modifications. Accordingly, genistein increases intracellular Ca^{2+} levels, Ca^{2+} transients and myofilament sensitivity to Ca^{2+} . Thus, genistein exposure enhances cardiomyocytes contractility [105]. The inward rectifying K^+ current contributes to the terminal phase of action potential repolarization and to maintain the resting membrane potential in cardiomyocytes. Exposure to genistein inhibits inward rectifying K^+ current, which can also lead to an abnormal function of cardiomyocytes [106].

cAMP-dependent chloride currents are critical in cardiomyocytes excitation-contraction coupling. It has been shown that cAMP-regulated cystic fibrosis transmembrane regulator (CFTR) Cl^- currents can be induced in guinea-pigs cardiomyocytes by genistein application, in a TK inhibition-independent way that requires prior PKA activation [107]. Furthermore, in the presence of a β -adrenergic agonist, genistein increased (i) the sensitivity of cAMP-regulated CFTR Cl^- , (ii) cAMP-regulated delayed rectifier K^+ current and (iii) L-type Ca^{2+} currents [107].

Several authors also described a cytoprotective effect of genistein against cell death. Genistein has an antiapoptotic activity against deleterious cardiac effects of arsenic trioxide, an anticancer agent used for

acute promyelocytic leukemia treatment. Intravenous injection of genistein in rat rescued long QT syndrome and dose-dependently improved arsenic trioxide-induced impairment of cardiac function. Moreover, pretreatment of RNVC with genistein before arsenic trioxide prevented mitochondrial membrane potential loss and inhibits JNK, p38-MAPK and caspase-3 activation [108]. Following an I/R injury, genistein is able to increase antiapoptotic BCL-2 expression and reduce BAX expression and caspase 3 activation. Likewise, genistein downregulates the expression levels of ER stress proteins, increasing cell viability of H9c2 cardiomyocytes [109]. Also, genistein effectively reverses glucose toxicity-induced mechanical malfunction in rat primary ventricular myocytes, a model that simulates diabetic cardiomyopathy [109]. In isolated guinea pig left ventricular papillary muscles, genistein stimulates myocardial contractility by inhibition of TK pathway and PI3K activity, but independently of the activation of β -adrenoceptor, the Na^+ – Ca^{2+} reverse exchange and the estrogen receptor [110].

Puerarin is an isoflavone derived from *Pueraria lobata* roots, commonly found as a Chinese herb medicine. Several studies showed that treatment of ventricular neonatal cardiomyocytes with puerarin decreases angiotensin II-induced ROS production. Likewise, puerarin suppresses the activation of ERK1/2, p38 and NF- κ B signalling pathways, limiting cardiac hypertrophy caused by angiotensin II [111]. It has been suggested that the anti-hypertrophic effect of puerarin occurs due to blocking of Rac1-dependent NADPH oxidase activation and AP-1 signalling pathway [112]. In addition, puerarin is able to block Na^{2+} currents in cardiomyocytes. Actually, results indicate that puerarin can block the inactivation state of the Na^{2+} channel and delay the recovery of the channel from its inactive state, suggesting a putative application as an antiarrhythmic agent [113]. Moreover, by upregulating BCL2-associated athanogene 3 (BAG3), puerarin enhances autophagy in RNVC, having an antiapoptotic effect against anoxia/reoxygenation injury [114].

Other isoflavones have been revealed as cardioprotective, for instance formononetin is the major isoflavone found in *Radix Astragali*, a Chinese medicinal plant widely used to treat cardiovascular diseases. It has been described that this compound reduces ROS formation, as well as mitochondrial damage, increasing cell viability of rat cardiomyocyte H9c2 cell line, after oxygen-glucose deprivation and reoxygenation [115]. Thus, by activating Akt and increasing glycogen synthase kinase-3 β (GSK-3 β) phosphorylation, formononetin enhances the interaction between phospho-GSK-3 β and adenine

nucleotide translocase, the mitochondrial permeability transition pore (mPTP) major component, which decreases mPTP opening and prevents apoptosis [115].

In a rat model of myocardial I/R injury genistein was tested for cardiovascular protection and inhibition of the inflammatory response. It was observed that it lowers myocardial necrosis and myocardial myeloperoxidase activity activity in the area-at-risk and in the necrotic area, decreases creatinine phosphokinase activity activity, increases myocardial contractility, decreases ventricular arrhythmias, reduces serum and macrophages levels of TNF- α and blunts cardiac intercellular adhesion molecule-1 (ICAM-1) expression in the injured myocardium [116]. Likewise, *in vitro*, genistein addition to peritoneal macrophages collected from untreated rats subjected to myocardial I/R injury (i.e. sham rats) significantly reduced TNF- α production, suggesting that genistein limits the inflammatory response and protects against myocardial I/R injury [116]. Moreover, genistein ameliorates pressure overload-induced cardiac dysfunction and interstitial fibrosis in mice [117]. In line with these observations, beneficial effects of genistin, a genistein glucoside, in rat myocardial I/R injury might involve reduction on oxidative stress and anti-inflammatory effects via suppression of the P2X purinoceptor 7 (P2X7)/NF- κ B axis [118].

Puerarin, when administrated orally at 100 mg/kg for 15 days, inhibits angiotensin II-induced cardiac hypertrophy via the redox-sensitive ERK1/2, p38 and NF- κ B pathways in mice. Moreover, puerarin significantly suppressed angiotensin II-induced increases in atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and β -myosin heavy chain (β -MHC) expression in the left ventricles *in vivo* [111]. Protective effects were confirmed *in vitro* by pretreatment of RNVC by 50, 100, and 200 μ mol/L of puerarin for two hours: a decrease in ROS production, protein synthesis and cell death were observed. Furthermore, puerarin significantly suppressed Ang II-induced activation of ERK1/2, p38 and the NF- κ B pathway proteins and the expression of ANP and β -MHC in cardiomyocytes. Next, it was proposed that puerarin effects could be mediated by Mir-15b/195 expression and suppressing non-canonical transforming growth factor beta (TGF β) signal pathway [119]. Recently, puerarin effects were extended to endothelial cells in angiotensin II-induced hypertensive rats [120]. Compared with control rats, angiotensin II-infused rats exhibited an impaired endothelium-dependent relaxation to acetylcholine

with reduction in the protein expression of phosphor-eNOS at Ser 1177 and an increase in the expression of gp91phox (85%), p22phox (113%), TGF β 1 (145%) and vascular cell adhesion molecule 1 (VCAM-1)(82%). Puerarin (100 mg/kg/day, IP once a day for 10 days) improved endothelium-dependent relaxation and reversed the changes in angiotensin II-induced protein expression of above molecules [120].

A meta-analysis on 11 human trials investigating the effects of isoflavones on BP concluded that soy isoflavone are effective in reducing both SBP and DBP in hypertensive subjects, but not in normotensive individuals [121]. Another meta-analysis of RCTs showed that isolated isoflavone consumption improved endothelial function [122]. Two meta-analysis also confirmed the blood cholesterol lowering effects of isoflavones [123, 124], although whether the effect is due to isoflavones or to soy protein is still controversial. Indeed, a more recent meta-analysis found no effects of isoflavones on blood lipids in hypercholesterolemic patients [125]. Not included in this meta-analysis, and important because of its length, is a 1-year RCT in post-menopausal women with the metabolic syndrome that showed reductions in SBP and DBP, improvements in blood lipids, fasting glucose and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) after supplementation with genistein (54 mg/day) [126]. Another 1 year study where cocoa flavanols and isoflavones (850 mg and 100 mg per day, respectively) were consumed daily by postmenopausal women with type 2 diabetes reported improvements in blood lipids, insulin resistance and insulin sensitivity [127], although no changes in BP or endothelial function were observed [128].

2.6 Anthocyanins

Anthocyanins are one of the most widely distributed colorants in fruits and vegetables. The main anthocyanins are delphinidin, cyanidin, pelargonidin, malvinidin, peonidin, and petunidin (for review: [129]). There are some studies indicating cardioprotective activities to anthocyanins enriched extracts but very few studies with pure anthocyanins (Table 6). Six anthocyanidins (aglycones) and seven anthocyanins (glucosides) effects against DOX-induced cardiotoxicity were investigated in H9c2 cardiomyocytes [130]. Cyanidin and delphinidin were the most potent in protecting against cytotoxicity,

as well as reducing the lipid peroxidation induced by DOX treatment. In contrast, seven anthocyanins showed little effect in cytoprotection and lipid peroxidation, although they markedly blocked intracellular ROS generation [130]. However, in the same cells subjected to simulated I/R and to tert-butyl hydroperoxide, cyanidin shows only a slightly protection and delphinidin no effect at 5 μ M. Importantly, higher doses were cytotoxic [130].

Anthocyanins cardioprotective activities have been largely demonstrated in animal models and humans [131], but the number of studies based on pure anthocyanins delivery is limited. However, it has been shown that anthocyanins such as delphinidin 3-*O*- β -rutinoside, cyanidin 3-*O*- β -rutinoside, delphinidin 3-*O*- β -glucoside, and cyanidin 3-*O*- β -glucoside are well absorbed and distributed to the blood in their intact form in rat and humans [132].

In addition to cytoprotective activity towards oxidative stress and anti-inflammatory activities, it emerged recently that anthocyanins can also target intracellular pathways and notably apoptosis and mitochondria at the level of respiration and of pro-apoptotic cytochrome *c* release (for review : [129]). For instance, it has been proposed that delphinidin could target Stat1 on the basis of *ex vivo* I/R experiments [133]. In addition, cyanidin 3-glucoside from purple corn was shown to ameliorate DOX-induced cardiotoxicity by a histological comparative study in mice [134]. More precisely, the effects of delphinidin 3-*O*- β -glucoside, cyanidin 3-*O*- β -glucoside and pelargonidin 3-*O*-glucoside on the activity of complex I of the mitochondrial respiratory chain were studied in mitochondria isolated from normal rat hearts and rat hearts subjected to ischemia [135]. Delphinidin 3-*O*- β -glucoside and cyanidin 3-*O*- β -glucoside, but not pelargonidin 3-*O*-glucoside, improved state 3 respiration and ATP synthesis in mitochondria after ischemia, suggesting that certain anthocyanins can act as electron acceptors at complex I and bypass ischemia-induced inhibition, resulting in increased ATP production after ischemia. For the first time this study revealed that pure anthocyanins could directly regulate mitochondrial energetic metabolism [135].

However, anthocyanins can also become toxic depending on their dose. For example, bilberry anthocyanins (0.01–1 mg/L) significantly attenuated the extent of I/R injury in isolated heart as evidenced by decreasing the release rate of lactate dehydrogenase, increasing the post-ischemic coronary flow, and by decreasing the incidence and duration of reperfusion arrhythmias. High concentrations (5–

50 mg/L) exhibited cardiotoxic activity despite having their radical scavenging and intracellular antioxidant capabilities increased in a concentration-dependent manner [136].

Few clinical studies with pure anthocyanin capsules have been conducted, mainly in diseased populations. Recent meta-analysis highlighted the evidence on the cholesterol-lowering effects of anthocyanins and anthocyanin-rich foods in dyslipidemic individuals [137-139]. The effects of pure anthocyanins on BP is yet unclear, and a recent meta-analysis of just 6 trials found no evidence of beneficial effects [140]. Very few studies have investigated the effects of pure anthocyanins on endothelial function, with only one study showing improvements in FMD after acute and 12 week consumption of 320 mg of anthocyanins per day in hypercholesterolemics [141]. Although the epidemiological and clinical evidence of the cardioprotective effects of berries is accumulating in the last few years [16], more studies with pure anthocyanins are needed in order to confirm that anthocyanins are indeed the bioactive compounds responsible for the effects.

3. *Stilbenes*

Resveratrol is undoubtedly the pure polyphenol that has attracted more attention and been most frequently evaluated for pharmacological and therapeutic implication in cardioprotection [142] (Table 7). This is due to its postulated role in the so-called “French paradox”, although the presence of resveratrol in the human diet is probably almost negligible [143, 144].

As previously said, cardiac hypertrophy is an adaptive heart response, nevertheless, whenever hypertrophy is chronic, there is a higher risk of HF and cell loss. RNVC were used to study whether resveratrol prevents hypertrophy and apoptosis induced by isoproterenol, a beta-adrenergic receptor agonist. Co-treatment of cardiomyocytes with resveratrol and isoproterenol reverted hypertrophy by decreasing cell surface and the expression of ANP that is a biomarker for hypertrophy [145]. Furthermore, resveratrol limited apoptosis induced by isoproterenol via partial inhibition of ER stress response protein expression, namely 78kDa glucose-regulated protein (GRP78), 94kDa glucose-regulated protein (GRP94) and CCAAT-enhancer-binding protein homologous protein (CHOP) [145].

In right ventricular rat myocytes, resveratrol treatment inhibits cardiac voltage-gated sodium channels, which is another mechanism by which it plays its cardioprotective and antiarrhythmic role [69].

Cardiac ischemic stroke generates heart lesion and tissue loss in particular during reperfusion phase. A protocol of anoxia (3h) and re-oxygenation (2h) was used in RNVC for evaluating the cytoprotective and anti-inflammatory role of resveratrol. Whenever, resveratrol is added to the cells immediately after re-oxygenation, there is a decrease of cell death, assessed by lactate dehydrogenase release and apoptosis assessed by caspase-3 activation, concomitantly with a reduction of pro-inflammatory factors, namely tumor necrosis factor (TNF- α) and interleukin (IL)-1 β [146]. Moreover, resveratrol decreased the expression of MiR-34a, which is a miRNA enhancing pro-apoptotic signaling and consequently, increasing cell death induced by anoxia/re-oxygenation in H9c2 cells [147].

In diabetes-induced cardiomyopathy, there is a significant correlation between hyperglycemia, oxidative stress and cardiomyocyte apoptosis. The pre-treatment of RNVC with resveratrol inhibited hyperglycemia-induced ROS generation and decreases NADPH oxidase activity, this effect being along with inhibition of apoptosis and increase of phosphorylation of AMP-activated protein kinase (AMPK) [148]. Furthermore, whenever AMPK is pharmacologically inhibited, there is a reversion of resveratrol beneficial effects revealing its essential role [149]. Using H9c2 cell line, resveratrol also reverts cardiotoxic effects of hyperglycemia by stimulating sirtuin 1 (SIRT1) [150]. In contrast, resveratrol prevented DOX-induced cell death in cardiomyocytes by activating of SIRT1 [151], as well as by phosphorylation of AMPK, which in turn prevents apoptosis via AMPK/p53 pathway [152].

Finally, resveratrol also modulates autophagic pathways which may limit apoptosis. Hydrogen peroxide-induced cell death was prevented by resveratrol via SIRT1 autophagy activation, involving Beclin 1, microtubule-associated protein 1A/1B-light chain 3 (LC3), p62 and lysosome-associated membrane protein 2a (LAMP2a)[153]

Bakuchiol, which is an analog of resveratrol (Table 7) and is found in the seeds of *Psoralea corylifolia*, limits cell death in isolated rat heart and cardiomyocytes challenged by I/R injury in a SIRT1 dependent manner [154]. In addition, bakuchiol significantly increased the activities of mitochondrial succinate

dehydrogenase, cytochrome c oxidase, and mitochondrial SOD and decreased the production of malondialdehyde [154]. Thus, bakuchiol is cardioprotective by targeting mitochondrial function in a SIRT-dependent way. Likewise, pterostilbene, which is a natural dimethyl ether derivative of resveratrol (Table 7), binds to the pocket of SIRT1 assessed by molecular docking analysis. Furthermore, it prevents cardiomyocyte death induced by I/R, upregulates SIRT1 expression, and whenever SIRT1 activity is inhibited, pterostilbene-induced cardioprotection is reverted [149].

In vivo, resveratrol has multiple effects such as a protective action of vascular walls towards oxidation, inflammation, platelet oxidation and thrombus formation [155]. Thus, resveratrol protects against LPS-induced cardiac dysfunction by enhancing sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a) activity through promoting the phospholamban oligomerization, the inhibitor of the Ca^{2+} pump in the sarcoplasmic reticulum [156]. Moreover, iron-overload injury and cardiomyopathy in acquired and genetic models is attenuated by resveratrol therapy [157]. Resveratrol can also ameliorate aging-related metabolic phenotypes and cardiac function by inhibiting some cyclic nucleotides phosphodiesterases (PDE), such as PDE4 [158]. In the heart, PDEs are compartmentalized enzymes that degrade the cAMP second messenger into inactive 5' AMP and are critically involved in pathogenesis of HF [159]. Park *et al.* showed that the metabolic effects of resveratrol in mice result from competitive inhibition of cAMP-degrading phosphodiesterases, leading to elevated cAMP levels. The resulting activation of exchange factor directly activated by cAMP 1 (Epac1), a cAMP effector protein, increases intracellular Ca^{2+} levels and activates the Ca^{2+} /calmodulin-dependent protein kinase kinase β /AMP-activated protein kinase (CaMKK β -AMPK) pathway via phospholipase C and the ryanodine receptor Ca^{2+} -release channel. As a consequence, resveratrol increased nicotinamide adenine dinucleotide (NAD^+) and the activity of SIRT1 and then, ameliorate the symptoms of metabolic diseases associated with aging [158].

As a model of diabetic cardiomyopathy, *db/db* mice were treated with resveratrol (0.3% mixed in chow) for 8 weeks. Resveratrol restored cardiac function, reduced cardiomyocyte apoptosis, and ameliorated ER stress via an activation of SIRT1 [150]. Unfortunately, it has been shown that the SIRT1 effect is not direct in this model, opening a still ongoing debate on the direct resveratrol target (s) [160, 161].

Resveratrol could also significantly improve cardiac dysfunction in many models of hypertension via effects on inflammation and oxidative stress and a plethora of molecular targets such as SIRT-1, AMPK, Nrf2, NF- κ B, endothelial nitric oxide synthase (eNOS) [143]. However, resveratrol could prevent cardiac hypertrophy and contractile dysfunction in simulated HR rats, i.e. spontaneously hypertensive rats without lowering BP [162]. This effect could be mediated by a reduction in oxidative stress.

Although the relevance of resveratrol as a beneficial dietary compound is very limited due to its low abundance in foods, and it is very unlikely that it will be responsible for the beneficial effects of berries and red wine, it has potential as therapeutic agent at pharmacological doses. For example, consumption of 150 mg of resveratrol or higher has been shown to reduce systolic BP, but not lower doses [163]. A meta-analysis of 7 RCT showed no effects on total cholesterol, HDL-C, LDL-C, and triglycerides, regardless of dose [164], whereas some positive effects were shown on glucose control and insulin sensitivity but only in diabetic patients [165]. Consumption of 75 mg of resveratrol daily for 6 weeks improved endothelial function in overweight individuals and an acute dose-response was reported in the same population [166, 167].

4. Phenolic acids

Phenolic acids have recently gained substantial attention due to their various biological and pharmacological effects, including cardioprotective effects (Table 8) [168]. Among other pure polyphenols investigated for its bioactivity, gallic acid is found in many plants and products such as tea leaves, grapes, blackberry, and gallnuts. It have been reported cardioprotective properties of gallic acid and gallates esters (Table 8) [169]. In RNVC and H9c2 cardiomyoblast cells, gallic acid decreases the isoproterenol-induced hypertrophy observed by a reduction of cell size and sarcomere organization. Moreover, the expression of the genes for β -myosin heavy chain, ANP and brain natriuretic peptide, markers of cardiac hypertrophy were also reduced [170]. Likewise, gallic acid was described to exhibit protective role against advanced-glycation end products (AGEs)-induced oxidative stress in cardiac cells. Exposure of cardiac H9c2 cells to AGEs resulted in an increase in ROS and decline in antioxidant enzyme levels and an increase in collagen content, an effect reduced by the free radical scavenging

activity of gallic acid [170]. This suggests a protective role against AGEs-induced cardiovascular complications. In a cardiotoxicity scenario induced by an organophosphate pesticide, gallic acid reveals protective properties in the cardiac stress in H9c2 cardiomyocytes by reversing cellular distortion, suppressing ROS levels and increasing collagen content [171].

In rat cardiomyocytes, ellagic acid reduces Ca^{2+} currents not by direct interaction with Ca^{2+} channel but through modulation of the nitric oxide-guanylate cyclase-cGMP pathways, and this effect could be useful in pathological conditions such as hypertension and ischemic heart diseases [172]. Moreover, caffeic acid and chlorogenic acid, compounds present in berries extract, are able to limit oxidative stress induced by hydrogen peroxide in chick embryo ventricular myocytes [173]. Furthermore, isoproterenol-induced oxidative stress in HL-1 mouse atrial muscle cell line was reverted by treatment with caffeic acid [174]. In RNVC, chlorogenic acid inhibits isoproterenol-induced cardiac hypertrophy by attenuating NF- κ B signaling pathway and suppressing ROS [175]. Moreover caffeic, chlorogenic and rosmarinic acids protected cardiomyocytes against DOX induced oxidative stress [176], at levels compared to dexrazoxan, used in the past as an antioxidant during DOX chemotherapy. Protocatechuic acid (PCA), a phenolic compound occurring in some food sources like açai palm fruit and mushrooms, has been found to possess various biological activities. In a RNVC model of I/R injury, PCA significantly inhibited the apoptotic rate and the expression of cleaved caspase-3, and it upregulated the expression of phosphorylated Akt therefore conferring cardioprotection [177]. PCA aldehyde, present in the root of *Salvia miltiorrhiza* (Lamiaceae), commonly known as Danshen in China, has been described as active against I/R injury [178]. PCA aldehyde administration markedly reduced cellular injury induced by simulated I/R in cultured RNVC, by involving the suppression of inflammatory response via inhibiting the NF- κ B signaling pathway. *In vivo*, PCA could provide a significant protection against myocardial I/R injury through regulation of the inflammatory response, platelet aggregation, and cardiomyocyte apoptosis [177].

Ferulic acid is present in Chinese medicinal herbs and exhibit pharmacological activities such anti-inflammatory, platelet aggregation inhibitory, antihypertensive and anti-apoptotic effects [179, 180]. In a daunorubicin-induced cardiotoxicity model in H9c2 cells, it was observed cellular protection by this

compound from the induced apoptosis through a mechanism that involves the interruption of the ERKs signalling pathway [181]. In a scenario of anoxia/reoxygenation injury, where induced intracellular Ca^{2+} overload is an important pathophysiological factor, it was observed that sodium ferulate attenuates this increase and improves cell survival in cultured cardiomyocytes through nitric oxide/cGMP-dependent protein kinase (cGMP/PKG) signal pathway [182].

Salvianolic acid B (SalB) is one of the major bioactive compounds from *Salvia miltiorrhiza*, whose roots are used in Chinese traditional medicine, and presents cardioprotective role against several different cardiac stresses and cardiopathies. In neonatal rat cardiomyocytes, angiotensin II-induced hypertrophy is reversed by SalB treatment via inhibition of poly (ADP-ribose) polymerase-1 (PARP-1) [183]. Furthermore, SalB decreases ROS generation by limiting NADPH oxidase 2 and 4 expression [183]. Likewise, exacerbated inflammation can also stimulate cellular stress and death in cardiomyocytes. Thus, in neonatal rat cardiomyocytes, LPS promotes inflammation as shown by TNF- α assessment and cell death measured by lactate dehydrogenase (LDH) release. Whenever cardiomyocytes are pre-treated with SalB, there is reversion of both effects by the activation of toll-like receptor 4 (TLR4)-NF- κ B-TNF- α pathway [184].

Prevention of autophagic process is also involved in SalB-induced cardioprotection. Indeed, in RNVC, 3h of starvation stimulates autophagy detected by increased levels of LC3II and apoptosis as shown by higher levels of caspase-8 and decrease in ATP concentration. Interestingly, co-treatment with SalB reverted autophagy and apoptosis, SalB acting on the crosstalk between both signaling pathways [185]. Likewise, SalB also limits autophagy and cell death in response to I/R by modulation of microRNA (miR) in a model of murine cardiomyocytes [186]. Actually miRs are endogenous regulators of gene expression and can play key roles in cell signaling. I/R promote the activation of autophagy and apoptosis and down-regulates miR-30a expression. In contrast, SalB reverts the suppression of miR-30a expression and limits autophagy and apoptosis in a PI3K/Akt pathway dependent manner [186]. Furthermore, whenever miR-30a is knocked down, SalB loses its cardioprotective role [186].

SalB also appears as an anti-apoptotic agent against cardiotoxicity induced by the anti-neoplastic drug arsenic trioxide. Indeed, SalB activates PI3K/Akt pathway and increases Bcl-2 and Bcl-XL expression, which in turn, prevents arsenic trioxide-triggered H9c2 cell death [187].

Finally, embryonic stem cell-derived cardiomyocytes were treated with high concentrations of glucose under hypoxia as an *in vitro* model for mimicking diabetes patients with cardiac ischemia. Under these conditions, there is an increase on the levels of hypoxia-inducing factor 1- α (HIF-1 α) and BCL-2 adenovirus E1B 19-kDa interacting protein 3 (BNIP3), which are hallmarks of hypoxia, and along with cleavage caspase-3 and cell death. Likewise, treatment with SalB decreases levels of HIF-1 α and BNIP3, limits activation of caspase-3 and prevents apoptosis [188].

In rats, SalB had anti-apoptotic and cardioprotective activities of following I/R by dual specificity protein phosphatase (DUSP)-mediated regulation of the ERK1/2/JNK pathway [189]. In combination with ginsenoside, SalB exerts also cardioprotection against I/R Injury in rats. Comparing with same dose of SalB or ginsenoside only, SalB- ginsenoside showed more significant effects on down-regulation of myocardial infarct size, maintenance of myocardium structure, improvement on cardiac function, decrease of cytokine secretion including TNF- α , IL-1 β , regulated on activation, normal T Cell expressed and secreted and the soluble cell adhesion molecules, sVCAM-1 [190]. Finally, a recent study revealed that SalB promotes neovascularization in the myocardium of ischemic rats [191]. Interestingly, in a rat model of isoproterenol-induced myocardial infarction, an oral pretreatment of vanillic acid, prevented an increase in creatine kinase-membrane bound in serum and diminished myocardial infarct size, showing the cardioprotective effect of the compound [192]. Moreover, vanillic acid prevented an alteration in lipid profile, induced a Bcl-2-associated X (BAX) expression decrease and a BCL-2 content increase [192]. This demonstrates a modulation of apoptosis signaling pathway and suggests that other cell death pathways (e.g. necrosis, necroptosis) have been prevented. Indeed, pharmacological inhibition of apoptosis and necroptosis would be more effective for cardioprotection [193, 194], but this remains to be investigated for vanillic acid. There are no described studies for phenolic acids supplementation in humans looking to cardiovascular outcomes.

5. Lignans

Plant lignans are polyphenolic substances derived from phenylalanine via dimerization of substituted cinnamic alcohols (see cinnamic acid), known as monolignols, to a dibenzylbutane skeleton. They are mainly found in various seeds, whole-grain cereals, and nuts but also to some extent in tea, vegetables, bread, coffee, fruit, and wine. A recent meta-analysis based on 3 independent studies do not reveal a positive impact on all-cause mortality and a contrasting impact on CVD [195-198]. Among the 4 dietary lignans identified, i.e. lariciresinol, pinoresinol, secoisolariciresinol, and matairesinol, only one pure compound, secoisolariciresinol was demonstrated to have potent angiogenic and antiapoptotic properties that may contribute to its cardioprotective effect in ex vivo and in vivo ischemic models (Table 9), putatively via increased protein expression of vascular endothelial growth factor (VEGF), Ang-1, and p-eNOS [199].

Moreover, dehydrosilybin, a flavonolignan from *Silybum marianum* (*Carduus marianus*) presented beneficial activities in cardiomyocytes (Table 9). In 2010, Gabrielová and colleagues demonstrated that low concentration of dehydrosilybin de-energized (decreasing mitochondrial potential) rat primary cultures of cardiomyocytes and attenuates rotenone-induced ROS formation [200]. Furthermore, in rat heart isolated mitochondria, it was verified by assessing oxygen consumption and mitochondrial potential that dehydrosilybin uncouples mitochondrial respiration and decreases mitochondrial ROS generation [200]. In a model of hypoxia/re-oxygenation dehydrosilybin also prevented cell death and oxidative stress in cardiomyocytes; in addition, dehydrosilybin treatment is associated with restored ratio of phosphorylated/total protein kinase C epsilon compared to injured cardiomyocytes [201].

6. Conclusion and perspectives

Several pure polyphenol compounds present cytoprotective effects when directly administrated in cardiomyocyte cultures. The most described biological process affected by polyphenols is apoptosis and its prevention. Likewise, pure polyphenol compounds also modulate intracellular Ca^{2+} levels, hypoxia-response pathways and autophagy. At the cellular level, polyphenol's ability to target numerous proteins involved in cardiac remodeling such as CaMKK β , Sirt1, BAX/BCL-2, PDEs, TRF2, eNOS as well as

SOD indicate that they can have multiple targets and complex effects. However, a key issue is the limited amount of information of polyphenol effects on structural proteins involved in cytoskeleton organization or proteins involved in excitation contraction-coupling, which have key roles in cardiac function. Moreover, consistent studies support a beneficial role of many pure polyphenols in treating various CVD in preclinical animal models, including I/R, myocardial infarction, LPS-induced cardiac dysfunction, hypertension, transverse aortic constriction, abdominal aortic constriction, diabetic cardiomyopathy and genetic models of cardiopathies.

Cellular and *in vivo* approaches are very useful for molecular mechanisms description but present a limited physiological relevance. In particular, in what concerns polyphenol concentration reaching heart tissue and the exact compound composition, whether the original compound present in plants reach tissue or the compounds reaching are its metabolites or derivatives. These limitations clearly hamper the translation of the *in vitro* and *in vivo* findings to the clinics and consumers. An emerging approach is the use of synthetic optimized polyphenols to favor a rational pharmacological development of drug candidates. For example, a new derivative of caffeic acid, the N-propyl caffeamide, has already shown *in vivo* cardioprotective effects and a good pharmacokinetic profile of N-propyl caffeamide against IR injury [202].

For human, based on the discussed literature (see above), it is clear that the cardioprotective potential of polyphenols is currently promising and deserves future studies in healthy patients, as well as CVD patients and cancer patients to prevent cardiotoxic side effects of anticancer agents. However, to date, few studies exist proving the effects of pure or purified polyphenols on human CVD risk biomarkers. Mixed results exist for the majority of the polyphenolic subclasses with very few dose-response studies conducted so far. Some available evidence suggest that polyphenols may have synergistic effects with other food components that enhance their efficacy and bioavailability, but more studies with pure polyphenols or combined with other compounds are needed to confirm that this is the case.

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Legend to figures

Figure 1. Vicious circle of risk factors and cardiovascular diseases. Five cardiovascular risk factors have been identified by the world health organization (i.e. unhealthy diet, obesity, physical inactivity, tobacco, alcohol). They can be influenced by diverse determinants such as poverty, stress, aging, gender and hereditary factors. All these factors and determinants contribute individually or synergistically to the progression of CVD, including coronary ischemic diseases (CID), myocardial infarction (MI) and heart failure (HF).

Figure 2. Classification of natural polyphenols. As a large and diverse family of compounds, polyphenols are into 4 subfamilies that share similar chemistry: flavonoids, phenolic acids, stilbenes, and lignans.

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Table 1-Cardioprotective evidence in cellular models, animal and humans for quercetin

Compound	Cellular models and primary cell cultures	Animal model	Humans
Quercetin	<p><i>Models of cardiac injury or toxicity</i></p> <ul style="list-style-type: none"> • ↑ viability [22] [23] [25]; • ↑PPAR- γ and AP-1 [26]; • ↓ TNF-α [22] ; • ↓ ROS overproduction [22]; • ↓ [Ca²⁺]_i overload [22]; • ↓ phosphorylation of JNK, and p38 [23]; • ↓ phosphorylation of MAPK-APK-2 and cleaved caspase [25]; • ↓ hypertrophy [26] [30]; • inhibition of BAX and caspase-3 [23] <p><i>Primary cell cultures</i></p> <ul style="list-style-type: none"> • ↓ hypertrophy [27] [29] 	<p><i>Transverse aortic constriction rodent model</i></p> <ul style="list-style-type: none"> • limited cardiac hypertrophy [32-35] [36]; • prevented cardiac dysfunction and hypertension [32]; • ↓ Heart rate [35]; • ↓ Cardiomyocyte Ca²⁺ oscillation frequency [35]; • ↑ SOD and eNOS activity [38]; • ↓ MDA and NADPH oxidase [38] 	<ul style="list-style-type: none"> • ↓ SB pressure [40] • ↓ DB pressure [40] • no significant effects in LDL-C, HDL-C or triglycerides [40] [41]

Table 2-Cardioprotective evidence in cellular models and animal for the main studied flavones

Compound	Cellular models and primary cell cultures	Animal model
Apigenin	<p><i>Lipoteichoic acid-induced inflammatory response in rat cardiomyoblasts [53]:</i></p> <ul style="list-style-type: none"> • ↓ ERK ½, p38, JNK and AKT phosphorylation in a dose-dependent fashion; • ↓ NFκβ translocation and modulation of COX-2 and IL-1β transcription and translation 	<p><i>ISO-induced myocardial toxicity in rats [54]:</i></p> <ul style="list-style-type: none"> • normal footing of hemodynamic, electrocardiographic parameters, endogenous antioxidant level and histopathological necrosis
Acacetin	<ul style="list-style-type: none"> • inhibition of the ultrarapid delayed rectified potassium current and the transient outward K⁺ current [55]; • prolongs action potential duration in human atrial myocytes [55] 	<p><i>Model of atrial fibrillation in dogs [55]:</i></p> <ul style="list-style-type: none"> • atrium-selective agent, effectively diminishing atrial fibrillation in anesthetized dogs
Scutellarin	<ul style="list-style-type: none"> • ↑ cell proliferation [46]; • ↑ expression of pro-survival proteins (BCL-2, VEGF, MM2 and MMP9) [46]; • ↓ Cytokines release (TNF- α, IL-1β, IL-6 and IL-8) [46]; • ↓ ROS and NO production [46]; • inhibition of high-glucose-induced monocyte endothelial cell adhesion [56]; • ↓ ICAM-1 and MCP-1 release [56]; • ↓ NF-kB expression [56] 	<p><i>Model of Alloxan-induced diabetic mice [56]:</i></p> <ul style="list-style-type: none"> • no effects on blood glucose levels

Table 3-Cardioprotective evidence in cellular models, animal and humans for the main studied flavanols

Compound	Cellular models and primary cell cultures	Animal model	Humans
Epigallocatechin-3-gallate (EGCG)	<ul style="list-style-type: none"> • ↓ oxidative stress markers (↑ SOD and catalase activities) [59]; • ↓ ROS and Ca²⁺ levels [61]; • inhibition of telomerase-dependent apoptotic pathways [60]; • anti-apoptotic properties (activation of (PI3K)/Akt pathway or via the phosphorylation of Stat1) [63] [64]; • ↑ contractibility of murine cardiomyocytes [66] [67] 	<p><i>ISO-induced myocardial toxicity in rats</i> [78]:</p> <ul style="list-style-type: none"> • prevented cardiac damages by maintaining the balance of anti-apoptotic / pro-apoptotic signaling proteins in the mitochondrial pathway of cell death; • ↓ oxidative stress; • ↓ inflammation; • protecting DNA integrity 	No studies
Catechin	<ul style="list-style-type: none"> • ↓ ROS and limiting DNA fragmentation [68]; • inhibition of cardiac voltage-gated sodium channels activity inhibiting cardiac voltage-gated sodium channels activity [69] 	No studies	No studies
(-)-Epicatechin	<ul style="list-style-type: none"> • ↓ cardiac hypertrophy Ang II-induced by activating the SP1/SIRT1 signalling pathway [76]. 	<p><i>Young spontaneously hypertensive rat model</i> [77]:</p> <ul style="list-style-type: none"> • ↓ blood pressure; • ↑ iNOS activity and ↓ in superoxide production in left ventricle and aorta 	<ul style="list-style-type: none"> • acutely improve endothelial function in healthy individuals [72, 79] synergistic effects between polyphenols and other dietary compounds exist [81] [82]

Table 4-Cardioprotective evidence in cellular models, animal and humans for the main studied flavanones

Compound	Cellular models and primary cell cultures	Animal model	Humans
Naringenin	<ul style="list-style-type: none"> • ↓ apoptosis (↓ER stress; normalized BCL-2, BAX and caspase 3; ↓lipid oxidation; ↑GSH; ↑ATF6, IRE1α and PERK for I/R insult and ↑ Akt, Nrf2 and caspase 3 towards oxidative insult) in injured H9c2 cells [85] [86]; • Cellular model of senescent myocardial cells [87]: ↓cellular senescence markers and modulate cardiac markers of aging-induced damage; • Naringenin and naringenin-7-O-glucoside Prevent DOX-induced cardiotoxicity [88] [30] [89] [90] 	<p><i>Pressure-overload-induced cardio hypertrophy model</i> [91]:</p> <p>↓ cardiac hypertrophy and interstitial fibrosis; ↑ left ventricular function. ↓PI3K/Akt, ERK and JNK signaling pathways</p> <p><i>Cardiorenal syndrome model</i> [92]:</p> <p>↓ cardiac remodeling and cardiac dysfunction; ↓ lipid profiles; ↓ inhibited cardiac inflammation; ↓oxidative stress; ↑ Nrf2</p>	No studies
Hesperidin	<ul style="list-style-type: none"> • ↓ apoptosis through ↑PI3K/Akt signalling pathway in primary cells after H/R injury [93]; • ↓ apoptosis in LPS-induced H9C2 cells via the JNK/Bax signalling pathway [94]. 	<p><i>I/R injury model</i> [96]:</p> <p>↓inflammation, ↓oxidative stress, ↓myocardial apoptosis</p> <p><i>LAD occlusion in diabetic rats:</i></p> <p>Cardioprotective activity</p> <p><i>Left ventricular remodelling model</i> [97]:</p> <p>↓inflammation, ↓myocyte apoptosis, attenuate cardiac dysfunction</p> <p><i>Pressure overload model</i> [203]:</p> <p>↓myocyte apoptosis, attenuated cardiac hypertrophy, fibrosis and dysfunction; ↓oxidative stress.</p> <p><i>Doxorubicin-induced cardiotoxicity</i> [204]:</p> <p>↓oxidative stress, abnormal cellular morphology and DNA damage in rat.</p>	<ul style="list-style-type: none"> • Endothelial function improvement in individuals with metabolic syndrome [99]; • ↓ systolic BP and improve acetylcholine-mediated vasodilation in overweight men [100]

Table 5-Cardioprotective evidence in cellular models, animal and humans for the main studied isoflavones

Compound	Cellular models and primary cell cultures	Animal model	Humans
Genistein	<ul style="list-style-type: none"> modulator of ionic channels mainly affecting Ca^{2+} signalling [104] [105] [106] [107]; ↓ apoptosis (prevented mitochondrial membrane potential loss, ↓ JNK, p38-MAPK and caspase-3 activation) preventing cell death against cardiotoxic arsenic trioxide [108]; ↓ ER stress proteins, ↑ BCL-2, ↓ BAX and caspase 3 in I/R injured H9c2 cells [109]; Reverses glucose toxicity-induced mechanical malfunction in myocytes, a diabetic cardiomyopathy model [109]; Stimulates myocardial contractility by inhibition of TK pathway and PI3K activity [110] 	<p><i>I/R injury model</i> [116]:</p> <p>↓ necrosis, myeloperoxidase activity, creatinine phosphokinase activity, serum and macrophages levels of $\text{TNF-}\alpha$, cardiac ICAM-1, ↑ contractility</p> <p><i>Pressure-overload-induced cardio hypertrophy model</i> [117]:</p> <p>↓ cardiac hypertrophy and interstitial fibrosis</p>	<ul style="list-style-type: none"> ↓ both SBP and DBP in hypertensive subjects, but not in normotensive individuals [121] and also in RCT in postmenopausal women with the metabolic syndrome [126]; ↑ endothelial function [122]; improvements in blood lipids in postmenopausal women with type 2 diabetes [127] and with the metabolic syndrome [126]
Puerarin	<p><i>Angiotensin II-induced cardiac hypertrophy:</i></p> <p>↓ ROS production; ↓ activation of ERK1/2, p38 and NF-κB, limiting cardiac hypertrophy [111];</p> <ul style="list-style-type: none"> anti-hypertrophic by blocking of Rac1-dependent NADPH oxidase activation and AP-1 [112]; block Na^{2+} currents in cardiomyocytes [113]; antiapoptotic: ↑ BCL2-associated athanogene 3 (BAG3); ↑ autophagy in RNVC, in anoxia/reoxygenation injury [114] 	<p><i>Angiotensin II-induced heart hypertrophy model:</i></p> <p>↓ cardiac hypertrophy via the redox-sensitive ERK1/2, p38 and NF-κB pathways in mice; restoring ANP, BNP and β-MHC expression in the left ventricles in vivo [111];</p> <p>↓ cardiac hypertrophy by ↑ Mir-15b/195 expression and suppressing non-canonical TGFβ signal pathway [119];</p> <p>Improved endothelium-dependent relaxation and reverted the changes in angiotensin II-induced protein expression of eNOS, TGFβ and VCAM-1 molecules [120]</p>	No studies

Table 6-Cardioprotective evidence in cellular models, animal and humans for the main studied anthocyanins

Compound	Cellular models and primary cell cultures	Animal model	Humans
Anthocyanins	<ul style="list-style-type: none"> • Cyanidin and delphinidin, the most potent anthocyanins in the protection against DOX cytotoxicity and ↓ lipid peroxidation in H9c2 [130]; • Delphinidin could target Stat1 on the basis of <i>ex vivo</i> I/R experiments [133]. 	<ul style="list-style-type: none"> • Cyanidin 3-glucoside from purple corn was shown to ameliorate DOX-induced cardiotoxicity by a histological comparative study in mice [134] 	<ul style="list-style-type: none"> • Cholesterol-lowering effects in dyslipidemic individuals [137-139]; • Improvements in FMD in hypercholesterolemics [141]

Table 7-Cardioprotective evidence in cellular models, animal and humans for the main studied stilbenes

Compound	Cellular models and primary cell cultures	Animal model	Humans
Resveratrol	<ul style="list-style-type: none"> • ↓hypertrophy (↓ANP and cell surface) in primary cultures [205, 206]; • ↓apoptosis (↓ caspase-3; ↓ER stress response proteins; ↑SIRT1; ↑AMPK phosphorylation; ↓miR-34a) in primary cells and cell lines [145], [146], [147], [148], [150], [151], [152]; • Antiarrhythmic role (↓cardiac voltage-gated sodium channels) in primary cells [69]; • Anti-inflammatory effect (↓TNF-α, IL-1β) in RNVC [146]; • ↓hyperglycemia-induced ROS and ↓NADPH oxidase activity (↑AMPK phosphorylation) [148]; • Modulates autophagy (via SIRT1) [153] 	<ul style="list-style-type: none"> • <i>Atherosclerosis rodent models</i> [155]: Protection against oxidation, inflammation, platelet oxidation and thrombus formation; • <i>Sepsis-induced cardiac dysfunction model</i> [156]: Protection by enhancing SERCA2a activity (via phospholamban oligomerization); • <i>Iron-overload-induced cardiomyopathy model</i> [157]: ↓pathological cardiac remodeling (myocardial fibrosis) and improvement of cardiac function Reestablishment of calcium homeostasis; • <i>Age-related metabolic and cardiac phenotype model</i> [158]: ↓cyclic nucleotides phosphodiesterases, e.g. PDE4 ↑NAD⁺ and SIRT1 activity (↑intracellular calcium; ↑CaMKKβ-AMPK pathway; ↑ryanodine receptor calcium release channel); • <i>Diabetic cardiomyopathy model</i>: ↓apoptosis; improve cardiac function, ↓ER stress (via SIRT1) [150]; • <i>Hypertension models</i>: ↓Inflammation and oxidative stress (SIRT1, AMPK, Nrf2, NF-κB, eNOS) [143] ↓hypertrophy and improve cardiac contractility [162] 	<ul style="list-style-type: none"> • ↓systolic BP [163]; • No effect on total cholesterol, HDL-C, LDL-C and triglycerides [164]; • ↑glucose control and ↑insulin sensitivity but only in diabetic patients [165]; • Endothelial function improvement in overweight individuals [166, 167].
Bakuchiol	<ul style="list-style-type: none"> • ↓cell death and modulates mitochondrial functioning (via SIRT1) in primary cells and isolated rat hearts [154] 	No studies	No studies
Pterostilbene	<ul style="list-style-type: none"> • ↓cell death (via SIRT1) in cell lines [149] 	No studies	No studies

Table 8- Cardioprotective evidence in cellular models and animal for the main studied phenolic acids

Compound	Cellular models and primary cell cultures	Animal model
Gallic acid	<ul style="list-style-type: none"> • ↓hypertrophy (↑ sarcomere organization, ↓β-myosin heavy chain, ↓ANP and BNP) in cell lines and primary cells [170]; • ↓ROS in cell lines [170] [171] 	No studies
Ellagic acid	<ul style="list-style-type: none"> • ↓calcium currents (via modulation of nitric oxide-guanylate cyclase-cGMP pathways) in primary cells [172] 	No studies
Caffeic acid	<ul style="list-style-type: none"> • ↓ROS in cell lines and primary cells [173] [174] 	No studies
Chlorogenic acid	<ul style="list-style-type: none"> • ↓ROS in primary cells [173]; • ↓hypertrophy (↓NF-κB and ↓ROS) [175] 	No studies
Protocatechuic acid	<ul style="list-style-type: none"> • ↓apoptosis (↓caspase-3) and ↑ Akt phosphorylation in primary cells [177]; • ↓inflammation (via NF-κB pathway inhibition [178]) 	<i>Myocardial I/R injury model</i> [177]: <ul style="list-style-type: none"> • ↓inflammation, ↓platelet aggregation, ↓cardiomyocytes apoptosis
Ferulic acid	<ul style="list-style-type: none"> • ↓apoptosis (interruption of ERKs signaling) in cell lines [181]; • ↑cell survival (↓intracellular calcium overload via nitric oxide/cGMP/PKC pathway) in primary cells [182] 	<i>Hypertensive model</i> [180]: <ul style="list-style-type: none"> • Anti-inflammatory, platelet aggregation inhibitor, antihypertensive, anti-apoptotic
Salvianolic acid B	<ul style="list-style-type: none"> • ↓hypertrophy (↓PARP-1) in primary cells [183]; • ↓ROS (↓NADPH 2 and 4) in primary cells [183]; • ↓inflammation and cell death (via TLR4-NF-κB-TNFα pathway) in primary cells [184]; • ↓autophagy and ↓apoptosis (↑miR-30a, ↑PI3K/Akt pathway) in cell lines and primary cells [185] [186] [187]; • ↓↓high glucose/ hypoxia-induced HIF-1α and BNIP3, ↓apoptosis (↓caspase-3) [188] 	<i>I/R injury model</i> : <ul style="list-style-type: none"> • ↓apoptosis (via DUSP-mediated regulation of ERK1/2/JNK) [189]; • in combination with Ginsenoside, ↓myocardial infarct size, maintenance of myocardial structure and improvement of cardiac function [176]; • in combination with Ginsenoside ↓ of cytokines' secretion (TNF-α, IL-1β, RANTES, sVCAM-1) [190]; • ↑neovascularization in the myocardium [191]
Vanillic acid		<i>Myocardial infarction model</i> [192]: <ul style="list-style-type: none"> • ↓creatinine kinase-membrane bound in serum and ↓myocardial infarct size; • ↓ alterations in lipid profile, ↓BAX, ↑BCL-2

Table 9- Cardioprotective evidence in cellular models, animal and humans for the main studied lignans

Compound	Cellular models and primary cell cultures	Animal model	Humans
Secoisolariciresinol	No studies	<i>Myocardial ischemic model</i> [199]: <ul style="list-style-type: none"> • ↓apoptosis; • ↑angiogenesis (↑VEGF, ↑Ang-1, ↑p-eNOS) 	<ul style="list-style-type: none"> • No positive impact of lignans on all-cause mortality and a contracting impact on CVD [195] [196] [197] [198]
Dehydrosilybin	<ul style="list-style-type: none"> • ↓mitochondrial potential, uncouples mitochondrial respiration and ↓mitochondrial ROS in rat heart isolated mitochondria and primary cultures [200]; • ↓cell death and ROS in primary cells [201]; • Restored the ration of phosphorylated/total protein kinase C epsilon in primary cultures [201] 	No studies	No studies